REMARKS

The amendments to the specification are made such that the specification correctly refers to trademarks, as suggested by the Examiner. Furthermore, the specification has been amended to recite the "new" address of ATCC.

The claims have been amended to correct typographical errors and to comply with suggestions of the Examiner.

Claims 1 and 8 have been amended to recite "heme oxygenase 1". This amendment corrects a typographical error in excluding "1". This amendment is not meant to limit the claim and is not in response to any rejection by the Examiner. The amendment is made merely to have the language of the claim reflect that of the specification and the other claims.

Claims 1 and 8 have also been amended to delete "or a functionally equivalent mutant thereof" and to restate the preamble.

Claims 3, 6, and 18 have been amended to contain proper antecedent basis.

Claims 10 and 17 have been amended to recite proper Markush language.

II. RESPONSE TO THE OFFICE ACTION OF APRIL 24, 2000

STATUS OF THE CLAIMS

Claims 1-28 are pending.

Claims 1-28 have been rejected.

Claims 1, 3, 6, 8, 10, 16, 17, and 18 have been amended.

SPECIFICATION

In the Office Action of April 24, 2000, the Examiner noted that the trademarks "WALL STENT", "RED KIT O", "ANNEXIN-V-FLUOS", "FACSCAN", and "MACLAB 400" were not properly capitalized. Applicants have amended the specification to correctly capitalize these trademarks.

Also, Applicants have amended the specification to indicate the new address of ATCC, as requested by the Examiner.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-28 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner believes that a skilled artisan would have to practice undue experimentation to enable the full scope of the claims (page 5, paragraph g). Applicants respectfully disagree.

Many factors must be considered when determining if a disclosure satisfies the enablement requirement and whether experimentation is "undue." MPEP 2164.01(a). In the Office Action of April 24, 2000, the Examiner describes the factors he considered in his determination.

In paragraph a, the Examiner stated that new methods would need to be developed other than those disclosed in the examples to reduce the claimed invention to practice. However, no evidence or reasoning is provided by the Examiner to explain why the exemplary embodiments would not work. Furthermore, the entire disclosure, not just the examples, must be taken into consideration. Pages 21 to 28 of the specification describe methods and instruments that may be used in the transfer of nucleic acids to the cardiovascular system of humans. For example, U.S. Pat. No. 5,674,192, which was incorporated by reference into the present specification, describes a device and method for delivering a nucleic acid to the wall of a blood vessel. In light of the present disclosure, one of ordinary skill in the art would understand how to use the methods or

devices described in U.S. Pat. No. 5,674,192 to inhibit vascular smooth muscle cell proliferation in a human.

Similarly, in paragraph b the examiner states "Limited prophetic guidance on the application of the method to other genes or other model systems or animal subjects has been provided"; however, such assertions focus entirely on the examples and do not take into consideration the entire disclosure. The Examiner appears to require prophetic examples, such a requirement is tantamount to requiring the Applicants to explain in detail how to use the invention in every different embodiment. To do so would essentially require the Applicants to teach an unskilled person how to use the invention. The specification is addressed to those skilled in the art. Such individuals, in light of the present disclosure, would understand how to apply the method using other genes or to other animal subjects than the exemplified system.

In paragraphs c-e, the Examiner cites several references to show that gene therapy is complex and associated with a number of problems. However, these papers discuss gene therapy as a whole focusing particularly on cancer therapy. There is nothing in the papers cited by the Examiner that states or suggests that a method of inhibiting vascular smooth muscle cell proliferation in a patient comprising administering to the patient an isolated nucleic acid encoding a heme oxygenase 1 gene is not possible. Indeed, preferred embodiments of the present invention overcome several of the shortcomings asserted by the Examiner, such as difficulty of targeting the vector to the desired site and low efficiency of delivery. By administering the composition containing the nucleic acid at high concentrations directly to the area of injury via a catheter or stent, the vector is targeted to the correct cell and delivery is efficient.

Finally, in paragraph f, the Examiner asserts that the findings of Deremaudt *et al.* demonstrate unpredictability of human heme oxygenase gene methods in cell culture and in gene therapy. Deremaudt *et al.* report that **endothelial** cells transfected with HO-1 grew faster than non-transfected **endothelial** cells. The present invention is to methods of inhibiting **vascular smooth muscle cell** proliferation. Endothelial cells are not vascular smooth muscle cells. In light of the present disclosure, at best, Deremaudt *et al.* merely indicates that HO-1 expression may have opposite effects on different cell types. Because the claims are not drawn to all cell types, Deremaudt *et al.* does not bring into question the predictability of the effect of HO-1 expression on smooth muscle cells.

The factors do **not** demonstrate (1) that the present disclosure fails to satisfy the enablement requirement and (2) that experimentation associated with the methods of the present invention is "undue." In light of the entire present disclosure, one of ordinary skill in the art would understand how to apply methods of inhibiting smooth muscle cell proliferation to cell culture and *in vitro* systems other than those of the working examples. Although gene therapy is complex, the working example showing efficacy in a well-established animal model for restenosis strongly indicates that the method is functional, despite problems others may have incurred in applying gene therapy to a disease. Finally, difference of effect of HO-1 expression in different cell types does not demonstrate that the effect of HO-1 expression in a particular cell type (vascular smooth muscle cells) is inconsistent. Thus, when all the factors are taken together, the methods and compositions of the present invention are enabled and do not require undue experimentation. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-28 were rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter that the applicant regards as the invention. Claims 1 and 8 as amended no longer recite a "functional equivalent." Applicants understand that, under the Doctrine of Equivalents, a claim reciting HO-1 will include functional equivalents to HO-1 and, therefore, the recitation of "functional equivalents" is redundant. Also, Applicants have included in claims 1 and 8 an indication of the result of the contacting or administering, respectively.

Claims 3, 6, and 18 have been amended to recite proper antecedent basis.

Claims 10 and 17 have been amended to recite proper Markush language.

The claims, as amended, particularly point out and distinctly claim the subject matter that the Applicants regard as the invention. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(A)

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (Lee) in view of Morita *et al.* (Morita) and Ali *et al.* (Ali). The Examiner alleges that Lee taught

a method of inhibiting smooth muscle cell proliferation by transfecting a smooth muscle cell with a human heme oxygenase gene in a liposome. However, Lee neither teaches nor suggests transfecting a smooth muscle cell. The reference demonstrates the effect of exogenous HO-1 expression in lung **epithelial** cells, not smooth muscle cells.

The difference between epithelial cells and smooth muscle cells is indicated in Wheater's Functional Histology, Burkitt *et al.*, Ed. Churchill Livingstone, Third Edition, 1996, pages 76 and 140 (Attachment A and B, respectively). Epithelial cells are extremely diverse and essentially cover or line all body surfaces including blood vessels (page 76, paragraph 1 and 5). A type of pithelial cells make up the endothelial layer of the blood vessel (page 140, paragraph 3). However, smooth muscle cells make up the tunica media of the blood vessel and are not classified as epithelial cells (page 140, paragraph 3). Thus, epithelial cells and smooth muscle cells are distinct and provide different functions.

Neither of the secondary references provides any motivation to replace the epithelial cell of Lee with a smooth muscle cell nor do they provide any expectation that such a replacement would yield a method of inhibiting the proliferation of the smooth muscle cell. Morita studied the effect of **endogenous** HO-1 expression in an *in vitro* co-culture system of smooth muscle cells and endothelial cells. The reference did not show or suggest that the endothelial cells (epithelial) are equivalent to smooth muscle cells. Also, Morita does not show or suggest contacting the smooth muscle cells with an exogenous HO-1 gene.

Furthermore, Morita did not show that expression of HO-1 in smooth muscle cells inhibited proliferation of the cells. Rather, the reference showed that endogenous HO-1 expression by smooth muscle cells prevents co-cultured endothelial cells from producing factors that cause the proliferation of smooth muscle cells grown in hypoxic conditions. In contrast, the present inventors show that expression of exogenous HO-1 in vascular smooth muscle cells leads to inhibition of proliferation in the cells, independently from endothelial cells. This is an important distinction considering that often in vascular injury the endothelial layer is missing from the blood vessel. If inhibition of vascular smooth muscle cell proliferation by HO-1 expression was dependent on the presence of endothelial cells, contacting the smooth muscle cells with a nucleic acid encoding HO-1 would not be effective in homogenous cultures of smooth muscle cells or in vascular injuries where the endothelial layer of cells have been removed from the blood vessel.

In summary, Lee demonstrates the effect of exogenous HO-1 in epithelial cells. However, epithelial cells and smooth muscle cells are different cell types that provide different functions. Therefore, the results in epithelial cells could not reasonably be extrapolated to smooth muscle cells. Morita merely shows that endogenous HO-1 expression in smooth muscle cells leads to inhibition of expression of mitogenic genes in endothelial cells. Taken together, the references cited by the Examiner do not teach or suggest contacting a vascular smooth muscle cell with a nucleic acid encoding HO-1. Therefore, Applicants respectfully request that the rejection of claims 1-7 under 35 U.S.C. § 103(a) be withdrawn.

REMARKS

Applicants believe the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned at (312) 321-4714 with any queries, comments or suggestions as to how to best expedite the above referenced application to allowance.

Respectfully submitted,

Thomas J. Wrona
Registration No. 44,410
Agent for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200

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